INPLASY PROTOCOL

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Review Stage at time of this submission: **Preliminary searches.**

Conflicts of interest:
None declared.

Cardiovascular adverse events in patients with kidney cancer receiving combination of angiogenesis inhibitors plus immune checkpoint inhibitors vs. angiogenesis inhibitors vs. immune checkpoint inhibitors: a network analysis of randomized controlled trials

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Review question / Objective: **The aim of this systematic review is to compare combination therapy with angiogenesis inhibitors plus immune checkpoint inhibitors vs. angiogenesis inhibitors vs. immune checkpoint inhibitors vs. mTOR inhibitors vs. placebo/no treatment in patients with advanced renal cell carcinoma (RCC) in terms of incidence and severity of cardiovascular adverse events to better inform clinical practice. To this end, the proposed systematic review will address the following question: Which is the best choice in terms of cardiovascular toxicity in advanced RCC, angiogenesis inhibitors plus immune checkpoint inhibitors vs. angiogenesis inhibitors vs. immune checkpoint inhibitors vs. mTOR inhibitors?**
Condition being studied: **This systematic review investigates incidence and severity of cardiovascular toxicities associated with anti-angiogenic and/or immune checkpoint inhibitors in RCC.**

INPLASY registration number: This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 12 December 2021 and was last updated on 12 December 2021 (registration number INPLASY2021120060).

INTRODUCTION

Review question / Objective: **The aim of this systematic review is to compare combination therapy with angiogenesis inhibitors plus immune checkpoint inhibitors vs. angiogenesis inhibitors vs. immune checkpoint inhibitors vs. mTOR**

inhibitors vs. placebo/no treatment in patients with advanced renal cell carcinoma (RCC) in terms of incidence and severity of cardiovascular adverse events to better inform clinical practice. To this end, the proposed systematic review will address the following question: Which is the best choice in terms of cardiovascular toxicity in advanced RCC, angiogenesis inhibitors plus immune checkpoint inhibitors vs. angiogenesis inhibitors vs. immune checkpoint inhibitors vs. mTOR inhibitors?

Rationale: As recently shown, anti-angiogenic agents are associated with increased cardiovascular risk in cancer patients compared to non anti-angiogenic therapies (Hou 2021, Journal of Cancer Research and Clinical Oncology), while no increased risk of cardiovascular events has been reported with immune checkpoint inhibitors compared to non immune checkpoint inhibitors (Agostinetto 2021, European Journal of Cancer). Several combinations of anti-angiogenic plus immune checkpoint inhibitors have been approved in renal cell carcinoma (RCC), including avelumab + axitinib, pembrolizumab + axitinib, cabozantinib + nivolumab, atezolizumab + bevacizumab. The assessment of the cardiovascular risk associated with combination anti-angiogenic + immune checkpoint inhibitors compared to that associated with anti-angiogenic or immune checkpoint inhibitors when administered as single agents or other molecular targeted agents may provide valuable information to personalize treatment choices in RCC.

Condition being studied: This systematic review investigates incidence and severity of cardiovascular toxicities associated with anti-angiogenic and/or immune checkpoint inhibitors in RCC.

METHODS

Search strategy: MEDLINE/PubMed and Embase will be searched using the MeSH term "Carcinoma, Renal Cell" and the Emtree term "renal cell carcinoma" using the restriction for randomized-controlled trials. No temporal restrictions are applied. Abstracts from the American Society of Clinical Oncology (http://asco.org/ASCO) and the European Society of Medical Oncology (http://www.esmo.org/ ESMO), for the period between 2004 and 2021 using the free text terms renal cell carcinoma/ cancer and randomized-controlled trial are also searched.

Participant or population: Patients with advanced renal cell carcinoma eligible for systemic treatment.

Intervention: Intervention may include the following: a) anti-angiogenic agents (biological drugs that include VEGF or VEGF receptors among their targets) as single agent or in combination with other agents; b) immune checkpoint inhibitors (biological drugs that include PD-1/PD-L1 or CTLA-4 among their targets) as single agent or in combination with other agents; c) mTOR inhibitors as single agents or in combination with other agents.

Comparator: Comparator may include the following: a) anti-angiogenic agents (biological drugs that include VEGF or VEGF receptors among their targets) as single agent or in combination with other agents; b) immune checkpoint inhibitors (biological drugs that include PD-1/PD-L1 or CTLA-4 among their targets) as single agent or in combination with other agents; c) mTOR inhibitors as single agents or in combination with other agents; d) placebo alone or observation.

Study designs to be included: Only randomized controlled trials will be included.

Eligibility criteria: The studies' inclusion criteria were: 1. Phase II and Phase III RCTs involving adult patients with renal cell carcinoma; 2. Trials that include as intervention and control arms as detailed in Items 13 and 14; 3. Trials' safety data of cardiovascular events and sample sizes must be available; 4. Trials must report on at least one of the following cardiovascular adverse events, which must be graded according to the Common Terminology

Criteria for Adverse Events (CTCAE) and will be assessed separately: a) hypertension; b) Cardiac disorders: atrial fibrillation; atrial flutter; atrioventricular block; cardiac arrest; conduction disorder; heart failure; left ventricular systolic dysfunction; myocardial infraction; myocarditis; congestive heart failure; cardiac ischemia; fatal cardiovascular incidences; QT prolongation; arrhythmias; c) arterial thromboembolic events; d) venous thrombosis. The exclusion criteria were: 1. Abstracts, reviews, non-randomized studies, animal and in vitro studies, meta-analyses, case reports, and subgroup analysis studies; 2. Elderly or pediatric population studies; 3. Studies that did not report any of the cardiovascular adverse events described above; 4. Unpublished Studies.

Information sources: We searched MEDLINE/PubMed and Embase. We used also searched abstracts from the American Society of Clinical Oncology (http://asco.org/ASCO) and the European Society of Medical Oncology (http://www.esmo.org/ESMO).

Main outcome(s): Cardiovascular adverse events represent the main outcome.

Additional outcome(s): There are no additional outcomes.

Data management: Titles and abstracts of studies retrieved using the search strategy and those from additional sources will be screened independently by two review authors (Verde and Buonerba) to identify studies that potentially meet the inclusion criteria outlined above. The full text of these potentially eligible studies will be retrieved and independently assessed for eligibility by two review team members (Cilio and Crocetto). Any disagreement between them over the eligibility of particular studies will be resolved through discussion with a third reviewer (Bardi). A standardized, pre-piloted form will be used to extract data from the included studies for assessment of study quality and evidence synthesis. Extracted information will include: study setting; study population and participant demographics and baseline characteristics; details of the intervention and control conditions; study methodology; recruitment and study completion rates; cardiovascular adverse events divided by type of event and severity); follow-up duration; information for assessment of the risk of bias. Two review authors (Verde and Buonerba) will extract data independently, discrepancies will be identified and resolved through discussion (with a third author E if necessary).

Quality assessment / Risk of bias analysis: Two reviewers (Cilio and Crocetto) will use the GRADE approach, as recommended by the Cochrane Collaboration (Higgins and Green, 2011), to classify the quality of evidence in each of the studies as 'high', 'moderate', 'low' or 'very low' on the basis of study design and the assessed risk of bias. Randomized trial evidence is classified as 'high'-quality evidence, but can be downgraded on the basis of the amount of bias reported. The same two reviewers (Cilio and Crocetto) will independently assess the trials' risk bias according to the Cochrane Risk of Bias Tool, and the following aspects will be evaluated: (1) random sequence generation (selection bias); (2) allocation concealment (selection bias); (3) blinding of participants and personnel (performance bias); (4) blinding of outcome assessment (detection bias); (5) incomplete outcome data (attrition bias); (6) selective reporting (reporting bias) and (7) other bias. Each aspect is evaluated as "high risk," "unclear risk," or "low risk."

Strategy of data synthesis: Network meta-analysis will be performed by considering either individual drugs (e.g. nivolumab, sunitinib, etc) or drug classes (immunotherapy, anti-angiogenetic agents). Network meta-analysis will be performed on the extracted dataset using a Bayesian approach. Risk Ratios (RRs) with 95% confidence interval will be used as summary statistic and will be modelled using the Markov chain Monte Carlo (MCMC) method. Three chains will be performed with at least 1000 iterations. Non-informative prior distributions will be used. Heterogeneity will be assessed using

both I-square statistics (less than 25% represents low heterogeneity, 25–50% represents moderate heterogeneity, and higher than 50% represents high heterogeneity) and Kendall's tau. For high heterogeneity studies, if appropriate, subgroup analysis or meta-regression will be performed. Both random-effect and fixed-effects model will be performed and evaluated in terms of fit and convergence. Effect sizes will be described with 95% credible interval. Bayesian model convergence will be tested with the Gelman and Rubin algorithm (Gelman & Rubin, 1996), while model fit will be assessed using Deviance Information Criterion (DIC). The consistency assumption between direct and indirect evidence will be tested comparing direct pairwise comparison estimates to the indirect results (node-splitting). All analyses will be conducted using R and in particular the gemtc R package. For all analyses, a p-value < 0.05 will be considered significant. The statistical analysis will be performed by prof. Pacella.

Subgroup analysis: Sub-group analysis will be performed according to line of treatment (peri-operative vs. first vs. later than first).

Sensitivity analysis: The sensitivity analysis aimed to determine whether the pooled RRs were stable or dependent on a single or a few studies included in the analysis will be conducted by recalculating the pooled RRs after having excluded each individual study.

Language: Only randomized clinical trials published in English will be considered for inclusion.

Country(ies) involved: This systematic review is conducted in Italy.

Other relevant information: None to be reported.

Keywords: Cardiovascular adverse events; renal cell carcinoma; anti-angiogenic therapy; immune checkpoint inhibitors.

Dissemination plans: We are going to publish the meta-analysis on a peer-reviewed journal and use social media and paper and online journal to propagate the results.

Contributions of each author:

Author 1 - Felice Crocetto - designing the review; coordinating the review; data collection; interpretation data; revise the protocol or review for important intellectual content.
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